UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: ***Wave 2 Cases***	

EXHIBIT
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General Prolene, Gynemesh PS, and Prolift Expert Report:

Peter Rosenblatt, MD

Background and Education

I am a physician licensed to practice medicine in Massachusetts and New Hampshire. I am certified by the American Board of Obstetrics and Gynecology and am also board certified in Female Pelvic Medicine and Reconstructive Surgery. I have been the Director of Urogynecology and Reconstructive Pelvic Surgery at Mount Auburn Hospital, in Cambridge, MA since 1995, when I founded the Division there. I have grown the Division to include five attending physicians and three clinical fellows. I was also the Director of Urogynecology at Beth Israel Deaconess Medical Center in Boston from 2000 – 2010. I am an Assistant Professor of Obstetrics, Gynecology and Reproductive Biology at Harvard Medical School and the Director of Urogynecology and Reconstructive Pelvic Surgery at Mount Auburn Hospital in Cambridge. I am a faculty member for the Mount Auburn Fellowship in Female Pelvic Medicine and Reconstructive Surgery and was the Fellowship Director from 1999-2009. I am also a faculty member for the Minimally Invasive Gynecologic Surgery Fellowship based at Newton-Wellesley Hospital and have been faculty for that fellowship since 2004. I have also been an oral examiner for the general boards for the American Board of Obstetrics and Gynecology (ABOG) since 2007, and as of 2016, I am now an oral board subspecialty examiner for Female Pelvic Medicine and Reconstructive Surgery. I have held several positions on

national medical organizations, and was on the Board of Directors of the American Urogynecologic Society from 2012 – 2014. I am currently on the Board of Directors of the Society of Gynecologic Surgeons, and hold the position of Assistant Secretary / Treasurer on the Executive Committee of that organization. I was on the Editorial Board for Female Pelvic Medicine & Reconstructive Surgery from 2010-2016, and am currently on the Editorial Board of the Journal of Minimally Invasive Gynecology. I am also an ad hoc reviewer for many peer-reviewed journals including Female Pelvic Medicine & Reconstructive Surgery, International Urogynecology Journal, Journal of Minimally-Invasive Gynecology, American Journal of Obstetrics and Gynecology, Journal of Urology, Menopause, and Neurourology & Urodynamics. I have co-authored dozens of articles in peer-reviewed journals, many of which concern pelvic organ prolapse and stress urinary incontinence. I have lectured locally, nationally and internationally on many subjects in the field of urogynecology and reconstructive pelvic surgery, including pelvic organ prolapse and urinary incontinence. I have also been a Principal Investigator for several independent as well as industry sponsored investigational studies on devices for pelvic organ prolapse and urinary incontinence and am currently the National Principal Investigator for one of the FDA-mandated 522 studies, specifically looking at a the safety and efficacy of a biologic graft for the treatment of anterior/apical vaginal prolapse.

I have also taught at many industry sponsored labs, including those organized by Ethicon, Bard, Coloplast, American Medical Systems, and Boston Scientific, the

purpose of which has been to instruct other surgeons on the proper use of surgical devices and tools to treat pelvic organ prolapse and stress incontinence. I have also worked as a consultant to many medical device companies in developing and validating new devices for the treatment of these same conditions. As part of that consulting, I have worked on developing Instructions For Use (IFU) documents to assist surgeons in the proper use of surgical devices and tools. In addition, I have worked closely with several companies of designing mesh products for transvaginal mesh, sacrocolpopexy mesh and mid-urethral slings. I hold 14 patents for medical devices, including 5 for a transobturator post-anal sling (TOPAS) I invented for the treatment of fecal incontinence, which I licensed to American Medical Systems (AMS) in 2007. Since that time, I have worked closely with engineers from AMS/Astora Women's Health in designing the mesh construct to meet the requirements of this indication as well as the insertion tools used for the procedure. I have been actively involved in testing the mechanical properties of the mesh and insertion tools in cadaveric specimens and in lab settings, as well as developing the IFU and other materials, including professional education presentations, on-line training, procedural videos and animations. I was also a surgical proctor for the Investigational Device Exemption (IDE) study on the TOPAS device, which was known as the TRANSFORM trial, the results of which were published in the February 2016 issue of the American Journal of Obstetrics & Gynecology.

Materials Reviewed

This report contains a summary of my qualifications, education, training, and experience, a complete statement of my opinions that I have formed to date, the basis for those opinions, and the information I considered in forming my opinions. All of my opinions are based on my education, training, clinical experience, the pertinent medical literature, discussions with colleagues and other materials I have reviewed. Materials that support my findings and opinions, including documents that I have reviewed, are identified either in this report or included in my reliance list which is attached to this report. My opinions are informed based on my continuous review of the literature over my career, as well as targeted literature searches.

Fee Schedule

review of medical records, deposition transcripts / telephone calls / preparation of report / travel	$800/hr
trial appearance &/or deposition testimony	$9000/day* (> 3 hr, including travel time) (plus expenses) $6000/ 1/2 day* (<3 hr, including travel time) (plus expenses) *Cancellation policy: 50% if canceled between 7-14 days prior to appearance. 100% if canceled less than 7 days prior to appearance
overnight travel	$2500 (plus expenses)

Expert Testimony Within Last 4 Years

Within the last four years I have testified as an expert in the cases of *Hayes v. Jordan; Vercher, Bryant, Smith v. Milhorat; Banks v. Witkowski; Watts v. Davidson;* and *Taylor-Ricci v. Coutinho and Staffier*.

Definitions and Background of Pelvic Organ Prolapse

My primary areas of focus are the diagnosis and management of pelvic organ prolapse, as well as urinary and fecal incontinence. I specialize in minimally-invasive surgery to treat these conditions and have done this type of work since completing my fellowship in Urogynecology and Reconstructive Pelvic Surgery in 1995. I have a very active surgical practice and perform approximately 300 surgeries for prolapse and incontinence each year.

Pelvic organ prolapse affects millions of women in the U.S., and it has been estimated that the lifetime risk for having surgery for either pelvic organ prolapse or stress incontinence is 20%. Over 200,000 women undergo surgery for pelvic organ prolapse each year in the U.S. In one study of multiparous women, 34% had a clinically evident cystocele, 18% had rectoceles, and 14% had uterine or vaginal vault prolapse. The pelvic organs are supported by, and enveloped within connective tissue, known as endopelvic fascia, which is attached to the bony structures of the pelvis, as well as to the pelvic floor muscles. Pelvic organ prolapse occurs when there is a deficiency in the support of the pelvic organs, such as the bladder, uterus and rectum. Injuries to the supporting muscles, fascia or ligaments of the pelvis may result in descent of one or more of these organs, leading to cystocele, uterine prolapse and/or rectocele, respectively. In addition, loss of support to the apex of the vaginal vault after hysterectomy may result in partial or total eversion of the vagina, which is known as vaginal vault prolapse. Finally, an enterocele is another type of prolapse that refers to the presence of small intestines

prolapsing through a defect in the endopelvic fascia, usually posterior to the vaginal apex. Mild degrees of pelvic organ prolapse may be asymptomatic; but when prolapse becomes symptomatic, women may experience pelvic pressure, bulging, or a sensation of a mass within or extending out from the vaginal opening. Prolapse may affect the ability of the woman to empty her bladder, leading to voiding dysfunction or urinary retention. Prolapse may also affect emptying of the bowel, and many women report incomplete emptying or the need to "splint", such as placing fingers in the vaginal area, perineum or buttocks to effectively empty their bowels. Although there are many potential causes of prolapse, the most commonly recognized etiology of prolapse is pregnancy and childbirth. Other risk factors for pelvic organ prolapse include advancing age, hysterectomy, menopause with reduction in systemic levels of estrogen, cigarette smoking, race and ethnicity, connective tissue disorders that lead to weakened fascia (e.g. Ehlers-Danlos syndrome, Marfan's syndrome), and conditions that cause chronic increased intra-abdominal pressure, such as asthma, COPD, obesity and constipation.

Treatment of Prolapse

There are several treatment options available to women with pelvic organ prolapse. Women with mild to moderate degrees of prolapse (usually Stage I-II) may choose not to actively treat the prolapse, and they may be monitored over time to see if there is any significant progression of their prolapse. If not, then continued expectant management may be all that is necessary. Some women choose to use a vaginal pessary, a plastic support device that can be worn for extended periods of

time, as long as their provider sees them on a regular basis to make sure the pessary is not causing problems, such as ulcerations or erosions of the vaginal walls. Other women choose to have surgical correction of the prolapse, as will be discussed below.

Surgical Treatments for Pelvic Organ Prolapse

There are many surgical approaches that can be used to manage pelvic organ prolapse, including vaginal, abdominal, laparoscopic or robotic. Each approach has its advantages and drawbacks, and the choice of approach is dependent on many factors, including surgeon training and experience, comparative success rates and risks, as well as the patient's medical condition and coexisting pathology. The transvaginal approach to prolapse is favored by many surgeons, as it is the least invasive, resulting in decreased pain and more rapid recovery from surgery. Transvaginal surgery has been used for over a century for prolapse repair. Common transvaginal procedures for prolapse include native tissue repairs, such as anterior and posterior colporrhaphy. In the anterior and posterior compartments, this usually involves plication of the stretched-out tissues after opening the vaginal wall and dissecting the underlying tissues away from the epithelium. There are several issues with this approach that may lead to failure of the repair. First, the tissues themselves are often weakened in patients who present with prolapse, and therefore they are prone to failure. Second, it has become apparent that these defects are often not due to a generalized thinning or distention of the anterior and posterior vaginal walls. Rather, anatomic studies have demonstrated that there are

site-specific defects that are responsible for the resulting herniation of the vaginal walls. Therefore, the process of plication does not take into consideration the site-specific nature of many cystoceles and rectoceles, which accounts for the high failure rate associated with these repairs. Several studies have shown that recurrence rates of prolapse after anterior and posterior colporrhaphy are in the order of 50-70%.[i] [ii] [iii] Vaginal apical suspensions, including uterosacral ligament suspension, McCall culdoplasty and sacrospinous ligament suspension can effectively treat uterine and vaginal vault prolapse, but also may fail if the patient's own tissues are weakened, which is often the case in women who present with symptomatic POP. The most common complication associated with uterosacral ligament suspension is ureteral obstruction, which has been shown to occur in up to 11% of cases.[iv] Sacrospinous ligament suspension can be a successful procedure to treat apical prolapse, provided that the apex of the vagina can reach the ligament without tension. This can be a problem in the post-hysterectomy patient, where vaginal foreshortening is not uncommon, and the apex of the vagina may not reach the ligament. It has been shown that this procedure leads to posterior deflection of the vaginal access, which may result in post-operative dyspareunia. In addition, studies have demonstrated that the posterior deflection of the vaginal access may lead to anterior wall prolapse.[v]

Use of Synthetic Mesh in Pelvic Reconstructive Surgery

Use of synthetic mesh is certainly not a new concept in pelvic reconstructive surgery. The high rates of failure after traditional prolapse surgery have led a great

deal of effort and innovation in the development of procedures that would provide long-term support, while maintaining safety and coital function and satisfaction for women. Prolapse procedures can be performed abdominally, which includes those procedures done through a laparotomy incision, as well as those done in a minimally-invasive manner, such as laparoscopic or robotic-assisted. As with transvaginal surgery, these procedures can be performed with or without mesh augmentation. The first reports of sacrocolpopexy date back to the 1950s in Europe when surgeons began to suture the posterior uterine fundus to the anterior longitudinal ligament of the sacrum. The most commonly performed mesh-augmented abdominal approach is sacrocolpopexy, where mesh is usually placed on the front and back of the vagina and then is attached to the sacrum. In the U.S., Lane was the first to describe abdominal sacrocolpopexy in 1962, when he advocated using in intervening graft between the vagina and the sacrum to overcome excessive tension.[vi]

Over the years, various modifications of the procedure were described, including extension of the graft along the full length of the rectovaginal septum, to decrease the chance of the graft detaching from the vaginal apex.[vii] Addison described using two separate strips of synthetic mesh, sutured to the anterior and posterior vaginal walls.[viii] Over the decades, various graft materials have been described for sacrocolpopexy, including Marlex, GoreTex, Mersilene, and more recently lightweight polypropylene. The move towards lightweight polypropylene was in response to reports of mesh exposures with less porous and multifilament materials

such as Mersilene and GoreTex. It is recognized that there are four types of synthetic material that can be utilized for pelvic organ prolapse surgery. In 1997, Amid described a classification system of synthetic materials for herniorrhaphies, based on porosity of the material, and that system is still in use today.[ix] Most experts currently recommend Amid Type I mesh for pelvic reconstructive surgery, which is defined as macroporous mesh with pore sizes greater than 75µ. The main disadvantage of sacral colpopexy had been the necessity of performing a laparotomy, with prolonged hospital stay and return to normal activities, not to mention potential wound complications such as infection and incisional hernia. More recently, minimally invasive sacrocolpopexy, including laparoscopic and robotic approaches have been described, although these approaches require extensive training and experience and not all patients are candidates for these approaches, due to medical comorbidities.

Transvaginal Mesh

In an effort to improve the success rate of transvaginal repairs, gynecologic surgeons started using permanent mesh to augment vaginal prolapse surgery. Use of synthetic grafts for transvaginal surgery dates back to the 1990s, when surgeons would cut pieces of flat mesh into custom shapes to conform to the individual patient's pelvic anatomy. It became clear in early studies that recurrence rates were significantly reduced with the use of synthetic mesh augmentation, although there was a tradeoff, in that there were certain complications, such as mesh exposure and, rarely, mesh erosion into neighboring organs that were unique to this type of

surgery. Other complications, such as bleeding, infection, injury to adjacent organs, pelvic pain and dyspareunia, have also been reported and are well-known risks of any pelvic floor surgery, including traditional native tissue repairs.

In terms of synthetic mesh, macroporous, monofilament, lightweight polypropylene mesh (Amid Type I) may be placed under the vaginal epithelium and attached to various structures in the pelvis, such as the levator ani fascia and muscles, and the sacrospinous and uterosacral ligaments, either anteriorly or posteriorly, to reinforce support of the endopelvic fascia.

My own experience with transvaginal mesh started in the early 1990s, as a resident in Obstetrics and Gynecology, when I was trained by Dr. Stephen Young to perform suburethral slings using Mersilene (polyester) mesh slings for stress incontinence, using the technique described by his mentor, Dr. David Nichols.[x] We published our center's experience with 110 women diagnosed with recurrent genuine stress incontinence, low-pressure urethra (commonly known as intrinsic sphincter deficiency), or those with chronically increased intra-abdominal pressure. We reported a high subjective and objective cure rate with exposure of the vaginal slang occurring in only two women.[xi] I was also performing open sacrocolpopexy at that time with Mersilene mesh. I continued to use Mersilene mesh for both suburethral slings and sacrocolpopexy as a fellow at Brown University in Providence, RI with excellent success rates and few mesh-related complications. When I completed my fellowship and went into practice in 1995, I continued to perform both these

procedures with Mersilene mesh. It was only with the introduction of TVT in 1998 that I changed my technique for suburethral slings, since there were significant advantages of TVT over Mersilene mesh slings, including reduced operating time, smaller incisions, lower overall morbidity and pain, and lower incidence of voiding dysfunction. In addition, it was apparent that there was no compromise in success rates, which has proven over the years to be long lasting. With more surgical experience and research on synthetic materials, it became apparent in the early 2000s that Type I mesh (monofilament, macroporous) was more appropriate for sacrocolpopexy as well, and I converted over to polypropylene mesh for that procedure as well. I began performing laparoscopic sacrocolpopexy in 2001 and have published two case series on my experience with a number of variations of this procedure. [xii] [xiii]

As stated earlier, mesh has also been utilized transvaginally in selected cases for women with symptomatic prolapse, who are at risk for failure of traditional, native tissue repair. I personally began using custom-fitted pieces of polypropylene mesh (including Gynemesh PS) in the early 2000s for both anterior and posterior repair, usually for advanced degrees of prolapse or in patients in whom I could not find adequate endopelvic fascia during surgical dissection. My practice has been to discuss the possible use of synthetic or biologic grafts with women pre-operatively, so that these options are available to me if the situation calls for tissue augmentation, and if the patient has agreed to their use. Before the introduction of vaginal mesh kits for prolapse, I would usually use a Capio needle driver to anchor

mesh to supporting structures in the pelvis, such as the sacrospinous ligaments or arcus tendineous fascia pelvis. When mesh kits became available, I began using them on selected cases since the devices used to insert the mesh into the proper position simplified the procedure, and I found that reduced operative time while maintaining excellent success rates for the patient.

It is important to remember that well before mesh kits came on the market, gynecologic surgeons were cutting flat pieces of mesh to fit the individual's anatomy and attaching these mesh pieces to various supporting structures in order to reduce the failure rate of prolapse surgery (i.e. reduce recurrent prolapse). The risks of mesh are well known, and have been well known for decades, whether the mesh is placed transvaginally or abdominally (open, laparoscopic, or robotic). Risks unique to mesh include the risk of mesh exposure and rarely, mesh erosion into surrounding organs, such as the bladder, urethra and rectum. Other risks that are often mentioned, including bleeding, infection, injury to adjacent organs, worsening or de novo urinary incontinence, urinary retention, pelvic pain, scarring and dyspareunia are risks that can be seen with any pelvic reconstructive surgery, whether or not mesh is used.

In October 2008, the FDA issued a Public Health Notification (PHN) regarding the use of transvaginal mesh (TVM).[xiv] They stated that surgeons and patients should be aware of "serious complications" associated with surgical mesh placed through the vagina, including mesh erosion and exposure. The PHN noted that over the previous

three years, the FDA had received "over 1,000" reports from nine surgical mesh manufacturers of complications that were associated with surgical mesh devices use to repair POP and stress urinary incontinence (SUI). They noted that the most frequent complications included exposure of the mesh through the vaginal epithelium, infection, pain, urinary problems, and recurrence of either the prolapse and/or incontinence. There were also less common reports of bowel, bladder, and blood vessel injury during insertion of the devices. The FDA made several recommendations including stressing the need for adequate informed consent and specialized training for specific mesh kits. They stressed the need to be vigilant for mesh complications including erosion and infection as well as complications associated with the tools used in the placement of the transvaginal mesh. They also recommended that surgeons inform their patients that implantation of surgical mesh is to be considered permanent and that some complications associated with the mesh may require additional surgery that may or may not correct the complication. Furthermore the FDA encouraged surgeons to inform their patients about potentially serious complications affecting their quality of life including pain during intercourse and vaginal scarring.

In 2011, the FDA issued a Safety Update based on a continuing analysis of adverse events reported to the FDA and complications described in the surgical literature.[xv] The Safety Update basically reiterated the information from the 2008 PHN, but went further by stating that the complications noted in the PHN were "not rare." They noted that from January 1, 2008 through December 31, 2010, the FDA had received

2,874 additional reports of complications associated with surgical mesh devices used to treat both POP and SUI. Of these, 1,503 reports were associated with POP repairs and 1,371 were associated with SUI procedures. With regards to POP repairs, in the same notification, the FDA stated that between 2008-2010, there were approximately 75,000 transvaginal mesh procedures performed annually in the U.S.[xvi] If one were to consider just the POP repairs, that would mean that there were 1,503 reports of complications over a period of time where 225,000 transvaginal mesh procedures were performed. That would imply that the rate of complication would be 0.007 or 0.7%, and the majority of the complications reported were mesh exposures, which are usually easily treated, either in the office or with a simply day surgical procedure under local anesthesia with or without sedation. One might argue that this is a gross underestimation since many (if not most) mesh exposures are not reported on the MAUDE (Manufacturer and User Facility Device Experience) database, since physicians are not required to report such complications. On the other hand, however, in order to make a statement regarding whether complications from TVM are rare or not, the FDA needed to base their statement on available statistics, and these are the only figures that were available for calculation at that time. For those reasons, it is my opinion that the FDA should not have made the statement that complications associated with TVM are not rare. In doing so, they opened the door to plaintiff attorneys who have now filed tens of thousands of cases within MDLs, primarily against medical device manufacturers of TVM devices.

The FDA conducted a systematic review of the published scientific literature to evaluate the safety and efficacy of transvaginal mesh for POP. This review demonstrated that transvaginal mesh repairs do not improve symptomatic results or quality of life over traditional non—mesh repair. The literature review revealed that mesh used in transvaginal repairs introduces risks not present in traditional non—mesh surgery for POP. There was no evidence that transvaginal repair to support the top of the vagina or the back wall of the vagina with mesh provides any added benefits compared with traditional surgery without mesh. Although transvaginal surgical repair to correct anterior wall defects with mesh may provide an anatomic benefit compared to traditional repair without mesh, this anatomic benefit may not result in better symptomatic results.

The primary outcome of six of seven RCTs referenced by the FDA[xvii,xviii,xix,xx,xxi,xxii,xxiii,xxiv] comparing TVM to traditional surgery for repair of the anterior compartment was anatomic cure. Of these six trials, only one failed to show superior anatomic correction of the anterior wall. These studies were not designed to detect differences in subjective outcomes, but that does not mean that objective outcomes should be discounted. To detect statistically significant differences in symptoms at just one year after surgery requires different study parameters than a study designed to detect differences in anatomic results. The only study of these seven RCTs that used a composite primary outcome of anatomic and symptomatic results did show a difference in both outcomes[xxv]. This trial, published in the New England Journal of Medicine, randomized 410 subjects (twice as many subjects as

the next largest study) to TVM vs. standard anterior colporrhaphy. The composite primary outcome showed superior results for TVM at 2 months and at 1 year. The symptom of vaginal bulge between groups was not different at 2 months, but at 1 year, 37.9% of the colporrhaphy group vs. only 24.6% of the TVM felt symptomatic bulging (P=0.008). The FDA also stated in the UPDATE from 2011: "There is no evidence that transvaginal repair to support the top of the vagina (apical repair) or the back wall of the vagina (posterior repair) with mesh provides any added benefit compared to traditional surgery without mesh". Of eight RCTs of TVM vs. non-mesh traditional surgery (reference above), only three were designed to investigate the apex as an outcome. All three failed to show a difference at the apex, but they also lacked statistical power to confirm that this failure was not the result of a type II error. One study was halted prior to reaching the necessary sample size, and another only had 14 subjects in the TVM arm. In fact, of the 287 subjects in these three trials, only six (2%) had apical failures. Therefore, apical failure (as defined in most RCTs) is not a very useful parameter to distinguish the anatomic success between pelvic organ prolapse procedures. With regards to the posterior wall, again, there are less data available compared to the anterior wall. Of the above-mentioned eight RCTs, only three included the posterior compartment as an outcome. Contrary to the FDA's above statement, one of these three (a study of recurrent prolapse repair) did show superiority of mesh over non-mesh repairs in the posterior wall at 1 year of follow-up (4.1% failure in the mesh vs. 24.5% in the non-mesh group, P=0.003). In summary, there has been a great deal of experience with transvaginal mesh repairs in the past decade among pelvic reconstructive

surgeons, both with flat sheets of mesh as well as kits designed for specific vaginal compartments. In addition to the studies mentioned above, there have been many abstracts and oral presentations at national and international meetings that support the use of transvaginal mesh in an effort to improve long-term outcomes of prolapse reparative surgery.

As part of a group of pelvic reconstructive surgeons called the "Pelvic Surgeons Network," I endorsed the article entitled "Time to rethink: an evidence-based response from pelvic surgeons to the FDA Safety Communication: 'UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse.'" The article reviewed the general statements made by the FDA in the 2011 Safety Update and exposed the weak evidence for their conclusions. In the summary of the article, it is stated that "The fundamental flaw in the FDA's analysis is that it is based on the question of proof of superiority of mesh in all patients. No one is suggesting that mesh is recommended for all patients. However, there may be instances when a surgeon suspects that a native tissue repair will have a high risk of failure and that the potential benefits of a mesh repair outweigh the risks. The purpose of this response is to demonstrate that TVM is an important tool in our surgical armamentarium that may be the best option in some cases. From our vantage point, it appears that the FDA has presented a biased view of TVM among all POP repair procedures because of the current reporting mechanisms in place."

Risks of Transvaginal Mesh

All surgery for pelvic organ prolapse and stress incontinence carries potential risks, including bleeding, infection, injury to neighboring organs (including the bladder, urethra, ureters, and rectum), blood vessels and nerves. There is always a risk of post-operative scarring and pain, including pain with intercourse. Other risks include urinary retention, prolonged catheterization, and the risk of failure or recurrent prolapse or incontinence. These risks exist whether mesh is used or not; all the aforementioned risks can occur with native tissue repairs alone. The only risks that are unique to mesh are the risks of mesh exposure (through the vaginal wall) or erosion (migration into neighboring organs, such as the bladder, urethra or rectum).

Most cases of mesh exposure are minor complications; in fact, the majority of mesh exposures are asymptomatic and are detected by gynecologists during post-operative or routine pelvic exams. They may also be symptomatic, and may cause vaginal bleeding, a vaginal discharge, or pain with intercourse, either for the patient or her partner. Treatment options include vaginal estrogen cream (which may resolve small exposures), excision of the exposed mesh fibers (which can often be done in the office for small and easily accessible exposures), excision of the exposed mesh in the operating room (usually done under local anesthesia), or simple observation with repeat examinations for asymptomatic patients. Complete excision of the implanted mesh is rarely required for small vaginal mesh exposures. When mesh removal is required for symptomatic exposure, it is usually a minor

procedure, and not life-threatening. In my experience, mesh exposures can almost always be successfully managed by undermining the vaginal epithelium, excising the exposed mesh, and reapproximating the vaginal epithelial edges without tension. In my professional opinion, it is rare that one needs to remove the entire mesh from the pelvis. Mesh straps that pass through areas such as the ischiorectal fossa or obturator foramen rarely cause any symptoms. It should be remembered that although a procedure may be required to manage vaginal mesh exposures, these are usually minor procedures and do not often recur.

In my professional experience, most complications associated with transvaginal mesh can be managed effectively without long-term sequelae, and not all complications require re-operation. Postoperative pain can often be managed with pelvic floor physical therapy, trigger point injections and oral or vaginal medications. A possible exception to this statement may be cases in which the mesh was improperly placed or tensioned. Although most improperly placed or tensioned mesh cases can be successfully treated (usually by resection of over-tensioned mesh arms), the improper placement or tensioning may have caused damage to nerves or other neighboring structures.

Many studies have been published in the literature on transvaginal mesh, both with custom-cut mesh from sheets, as well as commercially available mesh kits. There is quite a significant range of both success rates (objective and subjective) and complications, which implies that results are often dependent on the surgeon's

training and technique. Several surgical techniques are felt to be important for reducing complications in transvaginal mesh surgery. One important factor is the depth of dissection; a full-thickness dissection into the true vesico-vaginal space (for anterior repair) or rectovaginal space (for posterior repair) is important for reducing post-operative mesh exposure into the vagina. Experienced surgeons will usually perform hydrodissection in these spaces in order to assist sharp dissection. Placing mesh in a tension-free manner, without over-tightening the mesh arm attachments to surrounding structures, is also generally felt to be important in reducing the incidence of pelvic pain and dyspareunia.

The obvious advantage of using mesh for certain cases of prolapse is that the risk of recurrent prolapse is markedly reduced, compared to native tissue repairs. When one weighs the potential benefit of reducing recurrent prolapse (which may require another major operation to correct) with the potential risk of mesh exposure, one can see why pelvic reconstructive surgeons may recommend the use of transvaginal mesh in certain women with prolapse. Although there is no chance of mesh erosion or exposure with native tissue repairs, one must also consider the significantly higher rate of recurrent prolapse, which then may require a second and potentially more complicated re-operation for the prolapse.

Stability of Polypropylene

In my clinical experience, I have not seen any degradation of polypropylene fibers or mesh. I have searched the medical literature and have not seen any reliable

scientific literature that establishes any clinical significance to the debated surface cracking that has been under powerful scanning electron microscopy. In fact, a study plaintiffs' experts rely on by Clave (2010) found that "[s]everal hypotheses concerning the degradation of the PP are described below. None of these, particularly direct oxidation, could be confirmed in this study." Since polypropylene has been used for sutures for many decades, one would assume that we should see evidence of degradation of polypropylene when we re-operate on women who have had this material used in previous surgery. In over 20 years of surgery, I have not seen this to be the case. I also do not believe there is shrinkage of polypropylene mesh. It is well known that surgery of any kind may lead to scar tissue, which may contract. In other words, it is not the mesh that is contracting, but the scar plate that may contract to some extent. Polypropylene fibers and mesh do not have contractile elements; there is no scientific evidence that the fibers or the mesh itself undergoes any shrinkage of any kind.

Tissue Integration and Pore Size

Type I polypropylene mesh is macroporous, which allows the integration of the host's tissue into the mesh. This is apparent clinically whenever we need to make adjustments to mesh. For example, occasionally I will perform a "sling release" if a patient develops de novo urgency, urinary retention or prolonged voiding dysfunction after a mid-urethral sling. My experience has been that after 4-6 weeks, there is consistently excellent tissue integration within the mesh. Just as importantly, the pore sizes allow macrophages to enter within the structure of the

mesh during the healing phase so that any bacteria can be dealt with, preventing infection of the mesh. My experience is consistent with the vast body of clinical literature.

The Wound Healing Process

It is important to have a basic appreciation of how wound healing occurs to understand the role of transvaginal mesh in the post-operative healing process. Regardless of whether mesh is used or not, normal wound healing starts almost immediately after vaginal or abdominal surgery with swelling, inflammation, and the introduction of macrophages, which secrete proteins involved with wound healing. Epithelialization is a process that creates a superficial layer that acts as a barrier to infection, although it is thin and provides little tensile strength. The next process of wound healing involves the ingrowth of fibroblasts, which accumulate ground substance and lay down collagen, the primary structural protein of the body. This also stimulates "angiogenesis", the creation of new capillaries and blood vessels into the wound. Maturation of the wound occurs with cross-linking and remodeling of the collagen. Impaired wound healing may also occur under certain circumstances. Local tissue ischemia can impair the normal process of wound healing, preventing the normal mediators of tissue repair from participating in the wound healing process. Local tissue infection and necrosis may also disrupt wound healing.

As with any surgery, hematomas (collections of blood) may form under the incision during vaginal surgery. There are several potential outcomes of hematomas; they may simply liquefy and become reabsorbed over time by the body. Hematomas may also drain, potentially interrupting the incision. When vaginal mesh is present under the epithelium, this may lead to exposure of the mesh. Less commonly, hematomas become infected and form an abscess cavity.

Vaginal Atrophy and Mesh Exposure

Since many of my patients are menopausal, it is not uncommon for me to care for women who have signs of estrogen deficiency. This is especially relevant with vaginal atrophy, which is characterized by a loss of vaginal rugae, thinning of the vaginal wall, and a pale and shiny appearance of the vaginal epithelium. It is generally appreciated among pelvic reconstructive surgeons that postmenopausal women with vaginal atrophy undergoing surgery should, whenever possible, be pre-treated with estrogen in order to improve the quality and integrity of the vaginal wall. This is especially important when using synthetic mesh to augment the repair. It is generally accepted that vaginal atrophy is a risk factor for poor healing and potential mesh exposure through the vaginal wall. One common approach to treating vaginal atrophy is with vaginal estrogen, which may take the form of cream, vaginal tablet, or a plastic ring that slowly releases estrogen over a three-month period. In addition to being a risk factor for mesh exposure, vaginal atrophy in and of itself can cause or be contributing factors for other vaginal complaints and

conditions, including dyspareunia, recurrent urinary tract infections and vaginal bleeding.

The Use of Synthetic Mesh in Women with Fibromyalgia and Chronic Pelvic Pain

Fibromyalgia is a condition characterized by widespread musculoskeletal pain. Fibromyalgia is known to be much more common in women than men. By definition, patients with fibromyalgia must have symptoms for more than three months and the pain must be located at multiple sites both above and below the waist and on both sides of the body. It is believed that this disorder involves the amplification of painful sensations by affecting the way the brain processes pain signals. Fibromyalgia may be associated with chronic fatigue, feelings of decreased energy, sleep disturbances, and difficulty with remembering and concentrating. Although fibromyalgia is not a contraindication for transvaginal mesh surgery, it is generally appreciated that women with this condition may have an exacerbation of their pain after any kind of surgery, including vaginal surgery, with or without mesh. Since this is a musculoskeletal condition, surgery that involves attachment of mesh to the pelvic floor muscles may aggravate fibromyalgia. It is also generally appreciated by reconstructive pelvic surgeons that women with pelvic pain or tenderness of their pelvic floor muscles on exam may have an exacerbation of this pain with placement of transvaginal mesh. Therefore, many surgeons will exercise caution when considering the use of transvaginal mesh in women with pre-existing pain conditions, including chronic pelvic pain or fibromyalgia. These conditions are not,

however, contraindications to the use of transvaginal mesh, and I have used transvaginal mesh in this setting when I felt the potential benefits of transvaginal mesh outweighed the risks. It should also be noted that any pelvic surgery, including native tissue repair, has the risk of causing pelvic pain, dyspareunia, scarring, vaginal foreshortening, and injury to neighboring organs.

Post-operative Pelvic Pain

Regardless of pre-existing chronic pelvic pain, some women will develop post-operative pelvic pain, above and beyond the expected pain one would expect to experience after having had surgery. This is known to occur regardless of whether or not synthetic mesh has been used in the surgery. The most obvious cause of persistent post-operative pain is the development of scar tissue, which includes the development of intra-abdominal pelvic adhesions when abdominal surgery is performed. Scar tissue can also result in the retroperitoneal spaces, which is more typical after transvaginal surgery that does not involve entry into the peritoneal cavity. Vaginal foreshortening after hysterectomy, resulting in dyspareunia, is one example of post-operative scarring that can lead to persistent pelvic pain or discomfort. Myofascial pain, often originating in the levator ani muscles or obturator internus muscles, is another well-recognized cause of post-operative pain after any type of pelvic surgery, including hysterectomy and reconstructive pelvic surgery, whether or not synthetic mesh is utilized in the repair surgery. This is analogous to myofascial pain that many patients experience after orthopedic surgery, which requires intensive physical therapy to treat. Similarly, it is known that myofascial

pain may result from pelvic surgery, and can usually be diagnosed by palpation of the muscle groups of the pelvic floor. Myofascial pain can also result from over-tensioning of mesh straps in transobturator or transgluteal vaginal mesh surgery (such as the Prolift devices), as the mesh straps can pull on the pelvic floor muscles. A tension-free placement of the mesh straps, which holds the mesh in place without placing tension on the pelvic floor muscles, will avoid this type of pain. Fortunately, whatever the cause of the myofascial pain, in my experience, the majority of women who develop this condition can be effectively treated with pelvic floor physical therapy. Physical therapists who do this type of work will use myofascial trigger point release therapy, which is similar to a "deep massage" of the involved pelvic floor muscles, and often involves other physical therapy techniques, including core stabilization exercises and postural work. In my experience, many women with post-operative pain after transvaginal mesh surgery can avoid surgical revision by treatment with pelvic floor physical therapy. If physical therapy is ineffective or insufficient in relieving pain after transvaginal mesh implantation, surgical revision can be employed.

Position Statements

In 2011, the AUA published a position statement on the use of vaginal mesh for the repair of POP. They state "Like all surgical techniques, the incorporation of mesh into surgical POP repair has potential advantages and disadvantages. Mesh may improve long term anatomic results of surgery as compared to non-mesh repairs for some types of prolapse. Certain patients may benefit from mesh techniques, and the

use of mesh techniques should be a choice that is made after a careful discussion between surgeon and patient. Vaginal mesh placement for POP is associated with risks to the patient including vaginal extrusion, erosion, sexual dysfunction, urinary tract injury, pain and other complications. Like with all surgeries, these complications may be due to surgical technique, the materials utilized, patient anatomy, or a combination of factors. It is also important to recognize that many of these complications are not unique to mesh surgeries and are known to occur with non-mesh POP procedures as well." The AUA statement went on to state that there is "no convincing evidence that vaginal mesh placement can cause an autoimmune response, and there is no reason to remove vaginal mesh in asymptomatic patients."

Also in 2011, the American College of Ob/Gyn published a Committee Opinion entitled "Vaginal placement of synthetic mesh for pelvic organ prolapse." In this opinion, they made the recommendation that "Pelvic organ prolapse vaginal mesh repair should be reserved for high-risk individuals in whom the benefit of mesh placement may justify the risk, such as individuals with recurrent prolapse (particularly of the anterior compartment) or with medical comorbidities that preclude more invasive and lengthier open and endoscopic procedures."

In the same year, IUGA published a patient handout that addressed vaginal repair with mesh. It states that "currently available evidence suggests that surgery with mesh may be more effective than traditional surgery, in certain circumstances, in reducing the chance of recurrent prolapse." They do state that "there is not much

good evidence about how well this procedure works in the long term (over two years) and there is some concern regarding potential complications that are unique to permanent synthetic mesh placed through the vagina." In the section that discusses complications, it is stated that "with any operation there is always a risk of complications," and the complications more related to synthetic mesh implantations are listed as "mesh exposure" and "buttock and groin pain." They go on to state that "mesh exposure through the vaginal skin is not considered a major complication." They also list "chronic vaginal pain and painful intercourse" as a possible complication but state "the incidence of this complication is low and can occur following both mesh surgery and traditional surgery."

In 2013, AUGS released a position statement on Restriction of Surgical Options for Pelvic Floor Disorders. They state that "Non-mesh surgical treatment options also carry risks of surgical complications. No one approach has proven to be superior in all cases and it is particularly essential that specialists who regularly treat advanced and/or recurrent prolapse are able to maintain a complete set of treatment options in order to provide the most effective and individualized care. A ban on alternative surgical treatment interferes with the patient-physician relationship and withholds FDA acceptable options that the patient and her physician may decide is the best treatment option for her particular clinical situation." It is further stated that "There are certain clinical situations where many would agree the use of transvaginal mesh is not only acceptable, but preferred. Examples of these clinical situations include: patients with recurrent prolapse after a non-mesh, native tissue repair; or patients

where an abdominal approach may pose additional and potentially more significant surgical risks like patients with pulmonary co-morbidities or patients with known significant intra-abdominal adhesions. It is our strong opinion, that there are subsets of women with prolapse, and in some cases those with the most advanced disease, in whom the benefits of transvaginal mesh outweigh the risks and a blanket ban on the use of these products compromises patient care."

In 2013, AUGS and SUFU published a position statement on mesh mid-urethral sling for SUI. As stated in the position statement, "the polypropylene mesh midurethral sling is the recognized worldwide standard of care for the surgical treatment of stress urinary incontinence. The procedure is safe, effective, and has improved the quality of life for millions of women". "A broad evidence base including high quality scientific papers in medical journals in the US and the world supports the use of the MUS as a treatment for SUI. There are greater than 2000 publications in the scientific literature describing the MUS in the treatment of SUI. These studies include the highest level of scientific evidence in the peer reviewed scientific literature. The MUS has been studied in virtually all types of patients, with and without comorbidities, and all types of SUI. Multiple randomized, controlled trials comparing types of MUS procedures, as well as comparing the MUS to other established SUI procedures, have consistently demonstrated its clinical effectiveness and patient satisfaction. Among historical SUI procedures, the MUS has been studied as long in follow-up after implantation as any other procedure and has

demonstrated superior safety and efficacy. No other surgical treatment for SUI before or since has been subject to such extensive investigation."

In a joint committee opinion published in December 2011, ACOG and AUGS concluded that "Based on available data, transvaginally placed mesh may improve the anatomic support of the anterior compartment compared with native tissue repairs" but given the increased risk of complications recommended that "pelvic organ prolapse vaginal mesh repair should be reserved for high-risk individuals in whom the benefit of mesh placement may justify the risk, such as individuals with recurrent prolapse (particularly of the anterior compartment) or with medical comorbidities that preclude more invasive and lengthier open and endoscopic procedures" and that such procedures be performed by appropriately trained surgeons. The 2012 Cochrane Review: Surgical Management of Pelvic Organ Prolapse concluded that "The use of mesh or graft inlays at the time of anterior vaginal repair reduces the risk of recurrent anterior wall prolapse on examination. Anterior vaginal polypropylene mesh also reduces awareness of prolapse however these benefits must be weighed against the increased operating time, blood loss, posterior or apical prolapse and reoperation rates for mesh exposures associated with the use of polypropylene mesh". A review of more current studies from 2011 and 2012 suggest that transvaginal mesh placed by experienced mesh surgeons may have mesh erosion rates comparable to abdominally placed mesh. There are certain clinical situations where many would agree the use of transvaginal mesh is not only acceptable, but preferred. Examples of these clinical situations include: patients

with recurrent prolapse after a non-mesh, native tissue repair; or patients where an abdominal approach may pose additional and potentially more significant surgical risks like patients with pulmonary co-morbidities or patients with known significant intra-abdominal adhesions. It is our strong opinion, that there are subsets of women with prolapse, and in some cases those with the most advanced disease, in whom the benefits of transvaginal mesh outweigh the risks and a blanket ban on the use of these products compromises patient care. "The midurethral sling was not the subject of the 2011 FDA Safety Communication, "*Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Vaginal Placement for Pelvic Organ Prolapse*.". In this document, it was explicitly stated: "The FDA continues to evaluate the effects of using surgical mesh for the treatment of SUI and will report about that usage at a later date." In 2013, the FDA website stated clearly that: "The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year." I agree with the AUGS position statement that transvaginal mesh has an important role in treating women who are at risk of failure of native tissue repairs after appropriate counseling and informed consent.

Prolift Long-term Studies

Recent 7-year follow-up studies demonstrating the long-term safety and efficacy of Prolift have been published. [Meyer, JMIG 2016; Damoiseaux, IUJ 2015; Heinonen, IUJ 2016; Kozal, Canadian Urological Association 2014].

Meyer et al. (2016) reported 94% success at 7 years when using the hymen as the threshold for treatment success, and 84.3% of patients reported being somewhat or completely satisfied. The cumulative 7-year mesh exposure rate was 6.4%, all of which occurred in the anterior compartment, and these patients had discontinued using vaginal estrogen and presented with significant vaginal atrophy on examination. The authors reported that their results "suggest that mesh surgery does not negatively impact sexual function at long-term follow-up assessed using the PSID." The authors note that "dyspareunia is not unique to mesh augmentation; between 19% and 37% of patients report dyspareunia following traditional native tissue prolapse surgery."

Damoiseaux et al. (2015) published an RCT reporting 7-year follow-up data for Prolift versus conventional prolapse surgeries. The authors concluded "At 7 years follow-up the composite success rate of the trocar-guided mesh insertion appeared to be equal to native tissue repair in this group of patients with a history of recurrent POP." They also found that "the overall anatomic success rate was higher in the mesh group, which was particularly significant for the anterior compartment (74% vs. 31%, p 0.001)." Although the mesh exposure rate was higher than reported in most studies, this study found no statistical significance at 7 years in terms of pain (Prolift 34%; Conventional 45%; p = 0.241), chronic pelvic pain (Prolift 15%; Conventional 29%; p = 0.087), de novo pelvic pain (Prolift 21%; Conventional 32%; p = 0.200), dyspareunia (Prolift 27%; Conventional 25%; p = 0.801), de novo dyspareunia (Prolift 10%; Conventional 12%; p = 0.328); pain

during pelvic examination (Prolift 40%; Conventional 25%; p = 0.107), and vaginal discharge (Prolift 11%; Conventional 9%; p = 0.215).

Heinonen et al. (2016) reported 7-year follow-up data on 161 patients, and found that 80.1% of patients were satisfied with the procedure. 90.7% of patients were anatomically cured when defining cure as the leading descending point at the hymenal ring or above. The authors reported a 23% mesh exposure rate, however, the exposures were asymptomatic in 24 of 32 (66.7%) patients. Almost half of the patients (48%) initially received a Prolift because of recurrent prolapse. The authors addressed the unavoidable risk of mesh exposure as being a risk in all POP surgery using mesh, regardless of the operative approach. The authors noted mesh exposure rates in the literature from 6 to 19% after TVM, and after open sacrocolpopexy, "the exposure rate was 7.1%, and late onset exposure occurred in 4.8% of patients." Further, after the laparoscopic approach, "the exposure rate was 2.9 – 9% after 5 years." An important observation regarding the impact of factors other than the mesh on complication rates – such as patient factors, surgical technique, and surgeon experience – was that the authors' preliminary analysis showing how their mesh exposure rate decreased from 14% from the first 100 patients down to 5% with the following 95 patients.

Kozal et al. (2014) reported only 2 mesh retractions out of the 112 Prolift procedures performed, with a mesh exposure rate of 4.5% . The authors concluded that "Despite its market withdrawal, the Prolift system was associated with good

midterm anatomic outcomes and few severe complications." Although three patients reported better quality in sexual activity after surgery, nine patients (16.1%) reported de novo dyspareunia. This is not a unique complication of Prolift or mesh surgeries. The authors noted that the literature on using the vaginal approach to correct POP resulted in a 10-20% rate of de novo dyspareunia; 15% de novo dyspareunia after sacrospinous ligament fixation; 20% after myorraphy; and 7.8% after sacrocolpopexy. However, "[m]ultiple studies have not demonstrated any difference in surgery with or without meshes."

There are a number of studies evaluating the safety and efficacy of Prolift at 3-5 year follow-up. [Ubertazzi, IUJ 2015; Jacquetin, IUJ 2013; Miller, FPMRS 2011; de Landsheere, AJOG 2011; Benbouzid, Int J of Urology 2012; Wang, Arch Gynecol Obstet 2013]. Ubertazzi et a. (2015) reported patient satisfaction at 5-year follow-up of 80.3%, and 93.5% would recommend TVM surgery. Complications included de novo incontinence (1.3%), new onset dyspareunia (5%), mesh exposures (15.8%; half required surgical resection, while the other half were treated in the office and remain asymptomatic). The authors concluded that given the high patient satisfaction they achieved at 5-year follow-up, they "believe TVM to be a valuable asset for surgical correction of POP."

Benbouzid et al. (2012) reported 85.3% cure and 5.3% mesh exposure rate. They concluded that "the Prolift system is safe and efficacious for pelvic organ prolapse repair by transvaginal approach after 4.5-year follow-up."

Jacquetin, Cosson et al. (2013) reported outcomes from the French TVM 5-year prospective, multi-center follow-up in 82 of the 90 women enrolled. "A composite criterion of success defined as leading edge above the hymen (<0) and no bulge symptoms and no re-intervention for prolapse was met by 90%, 88% and 84% at the 1-, 3-, and 5-year endpoints respectively." The Prolift inventors reported 14 patients (16%) who experienced a mesh exposure, with 8 resections needing to be performed, and 7 exposures that were asymptomatic. At baseline, 54% of women were sexually active and remained so at 5 year follow-up. "De novo dyspareunia was reported by 10%, but no new cases at the 5-year endpoint." The authors discussed the difficulty in capturing sexual dysfunction information, and recommend "that sexuality should not be studied longer than 3 years in studies addressing POP surgery as the outcomes are no longer reflective of the impact of the surgery, but merely of the complexity of sexuality over time." Population-based studies prior to Prolift showed a significant number of women who have chronic pelvic pain and dyspareunia. [Jamieson, ACOG 1996; Mathias, ACOG 1996].

As the TVM authors set out in Table 1, there have been several randomized trials comparing polypropylene mesh with traditional native tissue repair. [Hiltunen, Sivalslioglu, Nieminen, Nguyen, Carey, Withagen, Altman]. These RCTs show a statistically significant improvement in cure rates associated with mesh (from 81-93%) compared to native tissue (48-72%), except for Sokol (2012), which showed an improvement but not statistically significant, and Carey (2009), which also

favored Gynemesh PS. In addition to the studies in Table 1, several other RCTs have evaluated Gynemesh PS or Prolift compared to traditional repairs, including, but not limited to: Halaska (2012) showing 83.1% cure for Prolift and 60.6% cure for traditional repair; Da Silviera (2014) showing 88% cure for Prolift and 81% cure for traditional repair; and Svabik (2014) showing 97.2% cure for Prolift and 38.2% cure for traditional repair.

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Table 1 Randomised controlled trials comparing polypropylene mesh with traditional native vaginal tissue repairs

Reference	Total number patients	Follow up (months)	Compartment studied	Anatomic cure mesh (%)	Anatomic cure traditional (%)	*p*
Hiltunen et al. [9]	104	12	Anterior	93	62	<0.04
Sivaslioglu et al. [10]	90	12	Anterior	91	72	<0.05
Nieminen et al. [11]	105	24	Anterior	89	59	<0.05
Nguyen and Burchette [12]	75	12	Anterior	87	55	<0.05
Carey et al. [13]	139	12	Anterior Posterior	81	65.6	0.07
Nieminen et al. [14]	202	36	Anterior	87	59	<0.0001
Withagen et al. [15]	194	12	All	90	55	<0.001
Altman et al. [16]	389	12	Anterior	82	48	0.008
Sokol et al. [17]	65	12	All	38	30	0.45

Miller et al. (2011) published the 5-year follow-up results from the U.S. TVM prospective, multicenter study. "When defined as treated side leading edge above the hymen, success rates were 89% at 5 years." Mesh exposure was found in 16 of 85 patients over the 5-year follow-up, with 9 partial mesh excisions. The authors reported that improvements in quality of life and improvement in prolapse symptoms were sustains over the 5-year period.

De Landsheere, Cosson et al. (2011) reported 3-year follow-up with 524 patients and concluded that "[r]ates of mesh complications and prolapse recurrence are relatively low in an experienced team." Mesh related complication was reported in

3.6%, mesh infection in 0.2%, mesh exposure rate of 2.7% (most presented within the first year), surgical intervention for prolapse recurrence was 3%, and severe symptomatic mesh retraction was found in 0.4% of the 524 patients.

Wang et al. (2013) reported 3-year follow-up cure rate of 93.3%, 6.25% mesh exposures, 5.7% recurrence, and a statistically significant improvement in quality of life compared to baseline as shown by improvement in PFDI-20, IIQ-7, and PFIQ-7 scores. The authors concluded that the "total Prolift system surgery represents a safe, simple and useful treatment for severe POP with satisfactory objective clinical outcomes." The authors stressed the importance of the Gynemesh PS properties used in the Prolift device, noting that "[Amid] type 1 synthetic polypropylene mesh has a lower potential for erosion than other types used in transvaginal repair surgery.

Safety and Efficacy

Level 1 evidence consistently show that prolapse repairs with Gynemesh PS are safe and effective. A 2016 Cochrane Review by Maher et al. reviewed 37 RCTs (4,023 women) and analyzed permanent mesh versus native tissue repair, absorbable mesh versus native tissue repair, and biologic graft versus native tissue repair. [Maher, Cochrane Library, 2016]. This 2016 Cochrane Review analyzed 25 RCTs comparing polypropylene permanent mesh versus native tissue, of which 17 RCTs compared anterior compartment repairs and 8 RCTs compared multi-compartment repairs. [Ali 2006; Al-Nazer 2007; Altman 2011; Carey 2009; da

Silveira 2014; Delroy 2013; De Tayrac 2008; De Tayrac 2013; Gupta 2014; Halaska 2012; Iglesia 2010; Lamblin 2014; Menefee 2011; Meschia 2004; Nguyen 2008; Nieminen 2008; Qatawneh 2013; Rudnicki 2014; Sivaslioglu 2008; Svabik 2014; Tamanini 2014; Thijs 2010; Turgal 2013; Vollebregt 2011; and Withagen 2011].

The 2016 Cochrane Review found in the permanent mesh vs. native tissue comparison that: "Awareness of prolapse at one to three years was less likely after mesh repair; Rates of repeat surgery for prolapse were lower in the mesh group; There was no evidence of a difference between the groups in rates of repeat surgery for incontinence; Recurrent prolapse on examination was less likely after mesh repair; and [t]here was no evidence of a difference between the groups in rates of de novo dyspareunia." However, when factoring in treatment for mesh exposures, the authors noted that "[m]ore women in the mesh group required repeat surgery for the combined outcome of prolapse, stress incontinence, or mesh exposure." This is not surprising given the risk of mesh exposure with any foreign body; however, this risk is well known to pelvic floor surgeons and is most often easily managed, either in the office setting or as a minor day surgical procedure. Some women with mesh exposures are asymptomatic and no specific treatment is needed. There is no evidence that excision of mesh in asymptomatic is necessary or prevents future problems. 19 RCTs with 1-3 year follow-up had an overall mesh exposure rate of 12%, with a mesh exposure rate of 10% in the anterior repair only studies. This is consistent with the 2011 updated Cochrane Review which evaluated 40 RCTs and found that "Native tissue anterior repair was associated with more anterior compartment failures than polypropylene mesh repair as an overlay or armed

transobturator mesh." [Maher, 2011]. The 2011 review found a 10% mesh exposure rate. "There were no differences in subjective outcomes, quality of life data, de novo dyspareunia, stress urinary incontinence, reoperation rates for prolapse or incontinence, although some of these data were limited." Dietz's 2011 review on sexual function found that "The use of mesh is associated with neither a worsening in sexual function nor an increase in de novo dyspareunia compared to traditional anterior colporrhaphy." Likewise, Maher's 2013 systematic review found that "Consistent level 1 evidence demonstrates superior subjective and objective outcomes following anterior transvaginal polypropylene mesh as compared to anterior colporrhaphy (grade A)." Barber (2013) published a review on the safety and efficacy of pelvic organ prolapse for vaginal apical prolapse surgery and concluded that "Polypropylene mesh is the preferred graft for ASC," and that "Vaginal procedures for vault prolapse are well described and are suitable alternatives for those not suitable for sacral colpopexy."

Abed's (2011) SGS systematic review found an overall mesh erosion rate of 10.3% described in 110 studies, and an overall dyspareunia rate of 9.1% reported in 70 studies. These rates were similar between synthetic and biologic grafts. They found that most graft erosions occur within 1 year of surgery, typically presenting with symptoms of "vaginal discharge, vaginal pain, and/or dyspareunia," although few more erosions can be detected with longer follow-up. Risk factors for vaginal graft erosion were "increasing patient age and concomitant hysterectomy and/or rectocele repair at the time of vaginal prolapse repair." "The majority of symptomatic mesh erosions (67%) required surgical excision either in the office or

in the operating room." Abed noted that dyspareunia and granulation tissue formation are not unique to mesh repairs, as "native tissue repairs may be complicated by dyspareunia and granulation tissue formation in a similar manner to what occurs with graft-augmented repairs."

Feiner (2008) published a systematic review to evaluate the efficacy and safety of transvaginal mesh kits in the treatment of prolapse at the vaginal apex in 30 studies (2,653 women), and found that the "overall objective success using transvaginal mesh kits in restoring apical vaginal prolapse is high." Mesh erosions (i.e. exposures) were the most commonly reported complication, occurring in 4.6-10.7% of women. Reoperations requiring anesthesia occurred at a rate of 1.5-6%, and reoperations not requiring anesthesia occurred at a rate of 0.4-2.3%.

Jia (2008) performed a systematic review evaluating the efficacy and safety of using mesh or grafts in surgery for anterior and/or posterior vaginal wall prolapse in 49 studies involving 4,569 women, which showed that "[n]onabsorbable synthetic mesh had a significantly lower objective prolapse recurrence rate (8.8%, 48/548) than absorbable synthetic mesh (23.1%, 63/273) and biological graft (17.9%, 186/1,041), but a higher erosion (e.g. exposure) rate (10.2% 68/666) than absorbable synthetic mesh (0.7%, 1/147) and biological graft (6.0%, 35/581)." The authors noted that "Mesh or graft repair is theoretically suitable for any degree of symptomatic anterior and/or posterior vaginal wall prolapse."

Diwadkar (2009) performed a systematic review and found that dyspareunia rates for traditional vaginal repairs, sacral colpopexy repairs, and mesh kits were similar at 1.5%, 1.5%, and 2.2%, and pain rates were 1.6%, 2.3%, and 2.5%, respectively. Total complication rates were also similar.

Sun (2016) compared patient outcomes of mesh repair and colporrhaphy for the treatment of anterior vaginal wall prolapse involving 11 studies (1,455 patients), and found no significant differences for the following complications: urinary retention, urinary incontinence, voiding difficulty, dyspareunia, urinary tract infection, and vaginal bulge. "Surgical repair with the mesh procedure appears to be a better choice for the treatment of anterior vaginal wall prolapse."

Mesh Exposure and Erosion Are Well Known Risks

Known risk factors for mesh exposure or erosion include: estrogen deficiency, improper dissection planes, poor tissue integrity, post-hysterectomy 'T' scar, subclinical infection, hematoma formation, increased mesh area ("mesh load"), and lack of integration of the mesh into the host tissue. [Kobashi, Sci World J 2009].

The types of mesh used for sacrocolpopexy have also evolved. The use of biologic grafts or cadaveric fascia has proven inferior to synthetic mesh.[xxvi] Mersilene, Marlex, and even Gore-Tex mesh, have been used in the past, but they have a much increased risk of infection and erosion compared to Ethicon's Prolene mesh, and more recently developed Gynemesh PS mesh. Rates of mesh exposure after

abdominal sacrocolpopexy procedures are reportedly low (between 3 to 5%), but these have been noted with only relatively short-term follow up. Nygaard has published a review showing mesh erosion rates from abdominal sacrocolpopexies to be as high as 12% and Nygaard's recent publication of the extended CARE study reported mesh erosion rate of 10.5% at 7-year follow-up. [Nygaard 2012].

TABLE 1:
Mesh Characteristics

Characteristic	GYNEMESH PS	PROLENE Mesh	MERSILENE Mesh
Thickness (in)	0.016	0.019	0.010
Unit Weight (mg/cm²)	4.36	7.60	4.22
Porosity (% of total area)	65.6	53.1	62.7
Burst Strength (psi)	115.82	234.33	82.92
Flexibility (mg/cm)	176.71	623.53	17.41
Tear Strength (lb)			
W (knitting machine axis)	4.41	7.32	1.23
C (across machine axis)	2.56	9.03	1.27
Suture Pull-Out (lb)			
W (knitting machine axis)	5.96	11.22	2.27
C (across machine axis)	6.55	13.88	2.06
Tensile Strength (lb)			
W (knitting machine axis)	21.67	50.48	26.37
C (across machine axis)	21.78	42.32	13.39

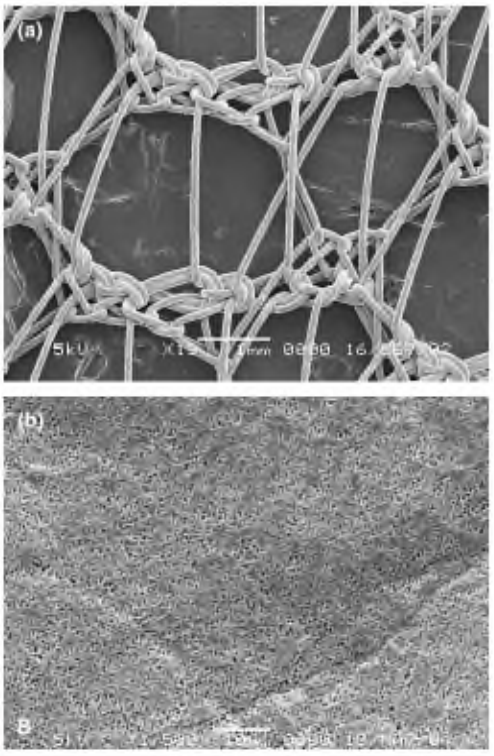

FIGURE 1. *A, Note the polypropylene mesh at a magnification of 19×. The scale bar is 1 mm demonstrating the large pore size of this mesh. B, Note the expanded polytetrafluoroethylene at a magnification of 1500×. The scale bar here is only 10 μm. The pores are all much less than 10 μm, which will not allow adequate host response. Photos courtesy of Ethicon, Inc.*

Some of the larger patient population Prolift studies describing mesh exposures include: Fatton (2007) reporting 4.7% mesh exposure out of 106 patients at 3 month follow-up; Meschia (2007) reporting 4.8% mesh exposure out of 228 patients at 6 months; Abdel-Fattah (2008) reporting 11% mesh exposure out of 219 patients at 3 months; Alperin (2008) reporting 4% mesh exposure out of 100 patients at 2 month follow-up; Altman (2008) reporting 1.6% mesh exposure out of 123 patients at 2 month follow-up; Cosson (2008) reporting mesh exposures in 3 patients (1.8%) when uterus had been preserved, 1 patient (2%) after previous hysterectomy, and 1

patient (4.3%) among patients with concomitant hysterectomy; Dedet (2008) reporting 2.6% mesh exposure out of 114 patients at 12 month follow-up; Lowman (2008) reporting 16.3% mesh exposure out of 129 patients at 7 month follow-up; Aungst (2009) reporting 3.8% mesh exposure out of 335 patients; Elmer/Altman (2009) reporting 26 (11%) mesh exposures out of 232 patients at 12-month follow-up, of which surgical intervention occurred in 7 cases and the remaining cases were all managed conservatively using topical cream; Ehsani (2009) reporting 2.2% mesh exposure out of 451 patients at 11 month median follow-up, of which 4 were treated surgically and the other 6 were managed conservatively with estrogen cream.

Depending on the type of mesh used to treat pelvic organ prolapse, non-absorbable synthetic, biologic or absorbable synthetic, the risks of associated scarring, contraction, risks to adjacent organs, mesh erosions or exposures, and pain or painful intercourse have been well known to gynecologists, urogynecologists, and urologists who operate in the pelvic floor. These risks are also well known as they have been described as extensively in the peer-reviewed medical literature. The bio-chemical properties of these implants are important but also each patient's own immune and histological reaction can also influence healing, scarring, short and long-term outcome similar to other prolapse surgeries. The Gynemesh PS mesh used in Prolift is not defective just because a small percentage of patients might experience mesh exposures or other well-known and acceptable complications.

Dyspareunia Is a Well-Known Risk

The medical literature commonly reports that 8 or 9 out of 10 women who have Prolift report that the Prolift surgery improved their quality of life. In order to accurately assess de novo dyspareunia rates, the baseline dyspareunia rates must be known, as well as how many patients with pre-existing pain experience resolution of dyspareunia after Prolift or POP surgery. Yesil (2014) reported an improvement of dyspareunia in 17.8% of patients at 12-month follow-up with a de novo dyspareunia rate of 10.7%. Studies have reported that women were satisfied with the outcome of their Prolift procedure even when they experienced a complication, such as mesh exposure or dyspareunia. For example, Feiner (2010) reported 4 patients with de novo dyspareunia and 21 women reported an increase in sexual intercourse after Prolift; however, 94% of women saying that they would have chosen to undergo the Prolift surgery again and 92% would recommend it to a friend. Similarly, Lowman (2008) concluded that despite having a 17% de novo dyspareunia rate after Prolift, "most would have the surgery done again." [Lowman, AJOG 2008]. In fact, over 75% of the patients reporting de novo dyspareunia described the pain as "mild or moderate," and most often occurring with insertion.

TABLE 4
De novo dyspareunia after prolapse surgery

Dyspareunia	ASC N = 224 (148)[a] Handa et al[21]	SSLF N = 287 (106)[a] Maher et al[6]	USS N = 110 (34)[a] Silva et al[27]	APR N = 165 (81)[a] Weber et al[18]	Prolift N = 129 (57)[a]
Baseline (preop) dyspareunia (%)	40.5 (60/148)	Unknown	20.6 (7/34)	8.0 (6/81)	36.8 (21/57)
De novo (postop) dyspareunia (%)	14.5 (11/76)	36.1 (22/61)	25.9 (7/27)	19.0 (14/75)	16.7 (6/36)

[a] Number sexually active preop.

Lowman (2008) described de novo dyspareunia rates across the POP literature as seen in Table 4, finding, "Overall, the prevalence of dyspareunia postoperatively with traditional prolapse repair ranges between 9-47%. The rate of de novo dyspareunia ranges between 14.5-36.1%. Thus, the rate of de novo dyspareunia in this study, although significant, is comparable to that reported with traditional pelvic organ prolapse repairs." For example, Holley (1996) reported 37.5% de novo dyspareunia after sacrospinous ligament fixation; David-Montefiore (2007) reported 15.8% postoperative dyspareunia attributed to concomitant perineorrhaphy; Nieminen (2003) reported 9% de novo dyspareunia after unilateral sacrospinous ligament fixation; Silva (2006) reported 25.9% de novo dyspareunia after uterosacral vault suspension; Weber (2000) reported 19% de novo dyspareunia after anterior colporrhaphy, posterior colporrhaphy, and/or vaginal vault suspension; Higgs (2005) reported 22% de novo dyspareunia after ASC repair; and Handa (2007) reported 14.5% de novo dyspareunia after ASC repair.

A 3-year study by Milani et al. (2012) evaluating the Prolift+M did not produce results much different from Prolift, as the authors reported 9% de novo dyspareunia and 14.8% mesh exposures. [Milani, IUJ, 2012]. Similarly, Quemener, Cosson et al (2014) concluded after comparing retrospective data on Prolift and Prolift+M that "a partially absorbable mesh does not seem to give advantages in comparison with classic non-absorbable mesh regarding rates of re-intervention." [Quemener, Eur J Obstet & Gynecol and Reprod Biology, 2014].

IFUs, Professional Education, and Patient Brochures

In addition to the IFU and Surgical Technique Guide, Ethicon made available to physicians the 2005 and 2007 Prolift Professional Education Slides as well as the 2007 Prolift Surgeon's Resource Monograph, which clearly demonstrate the proper placement of the guide and cannulas, and the tension-free placement of the mesh. These supplemental education documents also discussed the increased risks of adding a concomitant hysterectomy as well as mesh complications, including mesh exposure and erosion as well as dyspareunia and vaginal pain and many others, in addition to the treatment of complications.

The risks that were contained in the original Prolift IFU were appropriate because they warned of the adverse events reasonably associated with the use of the device. The same is true for the Prolene Mesh IFUs and the Gynemesh PS IFUs. [FDA Blue Book Guidance; Ethicon Standard Operating Procedure]. Frequency data was not necessary because the risks associated with the use of the device were well known to surgeons performing mesh-augmented pelvic floor repairs. The FDA Blue Book Guidance recommends providing frequency data only when "the data is not well known to the device user." Further, Ethicon's Standard Operating Procedure for Regulatory Labeling describes conveying information "specific to the type of device." More importantly, 21 CFR 801.109(c) permits medical device manufacturers to exclude information about "directions, hazards, warnings, and other information" that "are commonly known to practitioners licensed by law to use the device." Therefore, Ethicon did not have an obligation to warn of such well-known risks with

ANY pelvic floor surgery, such as acute or chronic pelvic pain, dyspareunia that could be temporary or permanent, death, mesh exposures that may be difficult to treat, failure of the procedure to work, the need for future surgeries to address an adverse event, painful intercourse for the patient's partner if the mesh is exposed, etc. These adverse events are commonly known to the practitioners who were licensed by law to use the Prolift. Further, Ethicon's patient brochures were appropriate for their intended purpose of initiating the patient-physician dialogue.

The adverse events that plaintiffs' experts suggest should be in the IFUs are are all commonly known risks that medical students, residents, fellows, and board certified pelvic floor surgeons are expected to already know, including the frequency and severity of those complications. Additional risks that are not included, such as those suggested by plaintiffs' experts that should have been included in the IFU, are commonly known, obvious risks for the surgeons performing these surgeries, and do not need to be included in the IFU per 21 CFR 801.901(c).

Ethicon's Professional Education materials communicated to surgeons additional information about the risks of the procedures. For example, the Prolift Monograph describes postoperative complications, including: hemorrhage, hematoma, fistula, infection, urinary retention, mesh exposure, mesh erosion, dyspareunia, and vaginal pain. Again, these are all commonly known adverse reactions of any pelvic floor surgery with or without mesh. Based on the risks that are commonly known ,

Ethicon's IFUs, Professional Education Materials, and Patient Brochures adequately warned pelvic floor surgeons who would be licensed to perform such procedures. All of my opinions are held to a reasonable degree of medical certainty.

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Peter L. Rosenblatt, M.D.

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